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Urinary Concentrations of Environmental Phenols in Pregnant Women in a Pilot Study of the National Children's Study

Mary E. Mortensen[a,*], **Antonia M. Calafat**[a], **Xiaoyun Ye**[a], **Lee-Yang Wong**[a], **David J. Wright**[b], **James L. Pirkle**[a], **Lori S. Merrill**[b], and **John Moye**[c]

[a]National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, GA

[b]Westat, Inc. Rockville, MD

[c]NCS Program Office, *Eunice Kennedy Shriver* National Institute for Child Health and Human Development, National Institutes for Health, Bethesda, MD

Abstract

Environmental phenols are a group of chemicals with widespread uses in consumer and personal care products, food and beverage processing, and in pesticides. We assessed exposure to benzophenone-3, bisphenol A (BPA), triclosan, methyl- and propyl parabens, and 2,4- and 2,5-dichlorophenol or their precursors in 506 pregnant women enrolled in the National Children's Study (NCS) Vanguard Study. We measured the urinary concentrations of the target phenols by using online solid-phase extraction-isotope dilution high performance liquid chromatography-tandem mass spectrometry. NCS women results were compared to those of 524 similar-aged women in the National Health and Nutrition Examination Survey (NHANES) 2009–2010, and to 174 pregnant women in NHANES 2005–2010. In the NCS women, we found significant racial/ethnic differences ($p<0.05$) in regression adjusted mean concentrations of benzophenone-3, triclosan, 2,4- and 2,5-dichlorophenol, but not of BPA. Urinary 2,4- and 2,5-dichlorophenol concentrations were highly correlated ($r=0.66$, $p<0.0001$). Except for BPA and triclosan, adjusted mean concentrations were significantly different across the 7 study sites. Education was marginally significant for benzophenone-3, triclosan, propyl paraben, and 2,5-dichlorophenol. Urinary concentrations of target phenols in NCS pregnant women and U.S. women and pregnant women were similar. In NCS pregnant women, race/ethnicity and geographic location determined urinary concentrations of most phenols (except BPA), suggesting differential exposures. NCS Main Study protocols should collect urine biospecimens and information about exposures to environmental phenols.

Keywords

Environmental phenols; Biomonitoring; National Children's Study; National Health and Nutrition Examination Survey; Pregnancy

Corresponding author: Mary Mortensen, MD, Division of Laboratory Sciences, MS F-20, 4770 Buford Highway, Atlanta GA, 30341, Phone: 770-488-7938, Fax: 770-488-4839, MMortensen@cdc.gov.

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1. Introduction

Humans are exposed to environmental phenols or their precursors through use of personal care and consumer products, consumption of processed food, and pesticide production or use. Bisphenol A (BPA) is primarily used to manufacture polycarbonate plastic and epoxy resins as well as polyvinyl chloride plastics and thermal paper. 2,4-Dichlorophenol has been used in the production of pesticides and herbicides and for the synthesis of pharmaceuticals and antiseptics. 2,5-Dichlorophenol is used in manufacturing dyes, pharmaceutical and agricultural products, and it is also the major metabolite of 1,4-dichlorobenzene used as a moth repellent and room deodorizer. Both chlorophenols are by-products of chlorination of municipal drinking water and industrial waste water (IPCS,1989). Benzophenone-3 is a commonly used sunscreen agent found in many cosmetic products (Gonzalez et al., 2006; Rastogi, 2002). Triclosan is a synthetic, broad spectrum antimicrobial agent used extensively in personal care and consumer products (Adolfsson-Erici et al., 2002; Bhargava and Leonard, 1996; Jones et al., 2000). Parabens such as methyl paraben (MP) and propyl paraben (PP) are widely used as antimicrobial preservatives in personal care products and pharmaceuticals, as well as in food and beverage processing (Andersen, 2008).

General population exposure to environmental phenols or their precursors is widespread and occurs via inhalation of ambient air, ingestion of food, beverages, and drinking water, and dermal contact with consumer products containing these chemicals. These compounds are rapidly eliminated in urine after being absorbed into the body, and exposure can be assessed by measuring each phenol in urine. Urine concentrations reflect recent (hours to days) exposure and may fluctuate during the day and between days, depending on the nature of the exposure (Teitelbaum et al., 2008; Ye et al., 2011).

Data from the National Health and Nutrition Examination Survey (NHANES), conducted by the Centers for Disease Control and Prevention (CDC), showed that non-occupational exposure to several environmental phenols is widespread in the U.S. general population, with benzophenone-3, BPA, MP, and PP detected in over 90% of the urine samples from NHANES 2003–2004 and 2005–2006 (Calafat et al., 2008a, 2008b, 2008c, 2010). Although adverse effects of exposure are largely unknown in humans, several environmental phenols are considered as endocrine disruptors based on *in vitro* and animal studies. Prenatal exposure to several environmental phenols or their precursors, assessed from urinary measurements of these compounds, has been examined in selected groups of pregnant women (Braun et al., 2009; Castorina et al., 2010; Smith et al., 2012; Wolff et al., 2008;Woodruff et al., 2011;Ye et al., 2008). Urinary concentrations of some phenols have been associated with birth weight changes in boys (Philippat et al., 2012; Wolff et al., 2008), risk of prematurity (Cantonwine et al., 2010), behavior in preschool aged children (Braun et al., 2009, 2011; Perera et al., 2012) but not in infants (Yolton et al., 2011), child wheeze (Spanier et al., 2012), and increased risk of undescended testis (Chevrier et al., 2012).

Aside from selected cohort studies and environmental exposure studies, limited biomonitoring data are available for pregnant women. We report environmental phenol exposures based on urine measurements in 506 women in their third trimester of pregnancy who enrolled in the Vanguard Study of the National Children's Study (NCS) during 2009–

2010. The sample, diverse geographically and economically, is one of the largest sets of biomonitoring data in U.S. pregnant women. We compare results from this convenience sample of NCS pregnant women with results from similar aged U.S. women in 2009–2010 and pregnant women in the U.S. in 2005–2010. We also show how these results compare with values reported in other published studies of pregnant women, expand the limited biomonitoring data available in pregnant women, and discuss how they may aid in planning the Main Study.

2. Methods

Study Populations

The NCS is a federally funded longitudinal study to prospectively investigate the effects of the environment on the health and development of U.S. children, following a cohort from before birth until 21 years of age. The environment is broadly defined to include such factors as air, water, diet, family dynamics, community and cultural influences, and genetics. The details of the history and activities of the Study are described elsewhere (www.nationalchildrensstudy.gov; Mortensen and Hirschfeld, 2012).

The original NCS Vanguard Study was a feasibility study, begun in 2009 to test the proposed recruitment, enrollment, and study visit assessment methodologies at seven sites. Two-stage recruitment was conducted in geographically defined areas (one or more counties or a census tract, depending on population size). First was door-to-door determination of eligible women ages 18–49 years, followed by questionnaire screening of eligible women to determine if they were pregnant. Second, pregnant women or those women trying to become pregnant were asked to participate. Of approximately 35,000 eligible women, 90% (30,900) were screened, and 63% (1950) of pregnant or trying-to-become-pregnant women were enrolled.

CDC proposed a collaborative pilot study with NCS in which the Environmental Health Laboratory at the National Center for Environmental Health would measure a number of environmental chemicals in biospecimens collected from a sample of Vanguard Study enrollees (pregnant women and infants). For phenols, we used a spot urine that was collected according to Vanguard Study protocol (identical at all sites), and shipped frozen to the NCS Biorepository, where specimens were aliquotted and frozen at −150°C, also according to NCS protocols (see Supplemental Material, available online) that were similar to NHANES urine collection protocols. The specimens were obtained at the third trimester visit from women who enrolled during 2009–2010 and consisted of a sample of about 70 women from each Vanguard Center study site. Specimens were stored at −20°C until they were analyzed. Available demographic information included age, race/ethnicity, annual household income (<$5000, $5000–$9,999, $10,000–$19,999, $20,000–$29,999, $30,000–$39,999, $40,000–$49,999, $50,000–$74,999, $75,000–$99,999, $100,000–199,999, and $200,000 or more), education (not high school graduate, high school graduate or some college, college graduate or higher), and study site. Written informed consent was obtained from all participants and the study protocol was approved by the NICHD Institutional Review Board (IRB) and the IRBs at each Vanguard Study institution. The involvement of

the CDC laboratory was determined not to constitute engagement in human subjects research.

NHANES has been conducted annually since 1999, releases data in two year cycles, and provides an ongoing assessment of health, health-related behaviors, nutrition, and environmental chemical exposures in the U.S. population (CDC, 2007). Using a stratified, multistage, probability cluster design, NHANES obtains a representative sample of the non-institutionalized U.S. population (additional detail is available at http://www.cdc.gov/nchs/nhanes.htm). Each year, approximately 6000 randomly selected residents across the U.S. are asked to participate through an advance letter, providing information that the household address had been selected as part of the NHANES sample. A field interviewer conducts screening and enrollment, and completes the household interview at the home; subsequent interviews, physical examination, and biological specimen collections are conducted at the Mobile Examination Center (MEC). The average participation rate for data collected at the MEC is approximately 80% (NCHS, 2013). Informed consent was obtained from all participants in the NHANES surveys prior to collecting any data or specimens, and the analysis presented here involved only de-identified data that were publicly available. Urinary phenols were measured in a single spot urine sample obtained from a subsample of the NHANES participants and shipped on dry ice to CDC's National Center for Environmental Health, where samples were stored at or below −20°C until analyzed by the Environmental Health Laboratory. Questionnaire response determined the month of pregnancy.

We used NHANES 2009–2010 phenols results for women ages 16–44 years for comparison to the NCS sample because the urine samples were collected during similar times and age ranges were the same. We used NHANES 2005–2010 results for pregnant women, ages 16–44 years as a comparison sample of U.S. pregnant women and combined results from multiple NHANES survey periods to obtain the largest number of pregnant women. We completed a trend analysis using multiple regression, adjusting by log transformed urine creatinine, age, and race/ethnicity and using NHANES survey cycle as a continuous variable. We used log transformed urine phenol concentrations in the model because the distribution was skewed. The purpose of this analysis was to identify significant changes in urinary phenol concentrations that might limit our comparisons.

Urine Analyses

Urinary phenols were measured by using online solid-phase extraction- high-performance liquid chromatography-isotope dilution-tandem mass spectrometry, as detailed by Ye et al. (2005, 2006). Limits of detection (LOD) were as follows: benzophenone-3 and BPA, 0.4 μg/L; triclosan 2.3 μg/L; MP 1.0 μg/L; PP, 2,4-dichlorophenol and 2,5-dichlorophenol, 0.2 μg/L. Urine creatinine measurements employed the Jaffé rate reaction performed on a Beckman CX3 Chemistry Analyzer (Beckman Instruments Inc., Brea, CA, USA).

Data Analysis

NCS data were analyzed using Statistical Analysis System (SAS, version 9.2; SAS Institute, Inc., Cary NC). NHANES data were analyzed using SAS (version 9.3.2; SAS Institute, Inc.,

Cary NC) and SUDAAN (version 10; Research Triangle Institute, Research Triangle Park, NC). SUDAAN calculates variance estimates after incorporating the sample population weights, nonresponse rates, and sample design effects. For each phenol, we calculated geometric mean and distribution percentiles both in μg/L and in μg/g creatinine. For concentrations below the LOD, we used a value equal to the LOD divided by the square root of 2 (Hornung and Reed, 1990).

Both NHANES and NCS participants provided self-reported race/ethnicity, age, and pregnancy trimester (only applicable for pregnant women in NHANES). A composite racial/ethnic variable was created to define three major groups: non-Hispanic black, non-Hispanic white, and Hispanic, and remaining women were categorized as 'Other'. Age in years at the time of the study visit (NCS) or at last birthday (NHANES) was used to stratify two groups: 16–29 and 30–44 years old. The groups were chosen to provide roughly equal age ranges.

We examined NCS results for each phenol by multiple regression analysis, using as covariates age, race/ethnicity, education, income, study site, and log urinary creatinine. Education (not a high school graduate, high school or some college, and college graduate or more) and income (<$50,000 or ≥$50,000) plus additional categories for missing education or income were included in the regression. Spearman correlations were evaluated among the urine phenol concentrations and among the regression covariates. Statistical significance was set at $p<0.05$.

3. Results

NCS

Demographic characteristics of the NCS sample and NHANES 2005–2010 and 2009–2010 women are shown in Table 1. The Vanguard Study site locations resulted in a geographically diverse NCS sample, and the women resided in counties with population densities ranging from about 40 persons per square mile to more than 20,000 persons per square mile (http://quickfacts.census.gov/qfd/index.html). Reported annual family incomes ranged from <$5,000 to ≥$200,000. Table 1 also shows that the NCS sample had a greater proportion of women who were non-Hispanic white, higher education (e.g., college graduate or higher), and higher income than the NHANES women.

Phenol detection rates among the 506 women ranged from 81% for triclosan to 100% for benzophenone-3 and MP. The overall geometric mean urinary concentrations are shown in Table 2, as are adjusted geometric means for race/ethnicity subgroups when race/ethnicity was statistically significant ($p<0.05$) in the regression analysis. Mean benzophenone-3 was highest in non-Hispanic white (72.0; 95% CI: 57.0, 90.9), followed by Hispanic (54.0; 33.9, 86.2) and non-Hispanic black women (23.0; 10.8, 48.7). Mean 2,4- and 2,5-dichlorophenol were highest in non-Hispanic black women, and were about 2 and 3.5 times higher, respectively, than in non-Hispanic white women. Hispanic women had the highest mean urine triclosan (33.9; 21.7, 63.0) compared to non-Hispanic black (14.2; 6.9, 29.2) or non-Hispanic white women (16.4; 13.1, 20.5). Urinary 2,4- and 2,5-dichlorophenol concentrations were highly correlated ($r=0.66$, $p<0.0001$).

Age and income were not significant covariates in any of the regressions (Table 2). Study site was significant; however, investigating geographical differences in urine phenols was beyond the scope of this analysis. Education was significant for benzophenone-3, triclosan, PP, and 2,5-dichlorophenol. We evaluated interactions of study site with each of the following: income; education; and race/ethnicity as additional predictors in the urine phenol regressions, but noted no significant findings.

NHANES 2009–2010

There were 524 women ages 16–44 years with urinary concentrations of phenols and creatinine, and demographics are shown in Table 1. Detection frequencies were >90% except for triclosan (77%).

The Supplemental Table shows results for NCS women and same-aged women in NHANES 2009–2010. In general, overall results appeared similar for the two groups. Differences as much as two times or greater were observed; however, wide confidence intervals indicate considerable instability in many of the results. NCS women ages 30–44 years had mean benzophenone-3 urinary concentrations that were about twice that of same-aged NHANES women (88.2 vs. 41.5 μg/L, respectively). Non-Hispanic white NCS women had higher mean urinary benzophenone-3 concentrations than their NHANES counterparts (89.6 vs. 38.0 μg/L, respectively). Compared to their NHANES counterparts, non-Hispanic black NCS women had lower mean MP and PP urinary concentrations (MP, 151.6 vs. 359.7 μg/L; PP, 25.3 vs. 57.0 μg/L) and higher mean 2,4- and 2,5 dichlorophenol urinary concentrations (3.8 vs. 1.4 μg/L; and 89.2 vs. 20.6 μg/L, respectively). Results in μg/g creatinine were similar (data not shown).

NHANES 2005–2010

There were 174 pregnant women with urinary concentrations of phenols and creatinine, and the unweighted sample demographics are shown in Table 1. The small sample size resulted in racial/ethnic groups that were too sparse for analysis, so only geometric means and medians for each overall group are shown in Table 3. A slight but significant decline ($p = 0.0002$) in triclosan urinary concentrations from 2005–2008 was noted in pregnant NHANES women (data not shown).

Geometric means for each urinary phenol appeared to be generally similar in the two groups of pregnant women (Table 3). Mean benzophenone-3 urinary concentrations were higher in the NCS women relative to pregnant women in the U.S. (59.5 vs. 38.9 μg/L, respectively), whereas mean 2,5-dichlorophenol urinary concentrations were lower in NCS women relative to pregnant women in the U.S. (3.9 vs. 5.6 μg/L, respectively). Results in μg/g creatinine were similar (data not shown).

Comparison to Other Results Obtained in Pregnant Women

Urinary concentrations of phenols have been measured in pregnant women (Braun et al., 2009; Cantonwine et al., 2010; Casas et al., 2011; Castorina et al., 2010; Fujimaki et al., 2004; Martina et al., 2012; Perera et al., 2012; Philippat et al., 2012; Shirai et al., 2013; Smith et al., 2012; Wolff et al., 2008; Ye et al., 2008) in the U.S. and abroad (Table 4). All

the pregnant women were of similar ages (largely 18–49 years old), with differences in the sample selection, race/ethnicity, demographics, and nationalities, to name a few. NCS and NHANES median BPA urinary concentrations (1.3 μg/L) for pregnant women were similar to other results in U.S. and Mexican women (Cantonwine et al., 2010) and lower compared to Spanish and French women, 2.2 and 2.7 μg/L, respectively (Casas et al., 2011; Philippat et al., 2012). In contrast, a small number of U.S. Old Order Mennonite women had the lowest mean urinary concentrations of BPA, 0.7 μg/L (Martina et al., 2012). Median urinary benzophenone-3 concentrations were approximately 8–33 times higher in the NHANES and NCS compared to the French and Spanish women (Casas et al., 2011; Philippat et al., 2012), whereas these European women had higher median urinary 2,5-dichlorophenol concentrations (16.5 and 10.2 μg/L, respectively) compared to the NHANES and NCS pregnant women (4.8 and 2.7 μg/L, respectively). The largely minority women in the Salinas Valley of California (Castorina et al., 2010) and New York City (Wolff et al., 2008) cohorts had the highest median urinary 2,5-dichlorophenol concentrations: 21.5 and 53 μg/L, respectively. This is consistent with our regression finding that Hispanic and non-Hispanic black women had higher 2,5-dichlorophenol concentrations than non-Hispanic white women (Table 2). These pregnant women also had median urinary 2,4-dichlorophenol concentrations that were about two to three times higher than the NHANES and NCS pregnant women. However, these medians are relatively consistent with the regression race/ethnicity adjusted geometric mean concentrations (Table 2). Median urinary MP and PP concentrations appeared generally similar among the groups in which these compounds were measured.

4. Discussion

We measured urinary concentrations of several phenols in a sample of 506 women in their third trimester of pregnancy enrolled in the NCS and found the results to be generally similar to those from pregnant women in NHANES 2005–2010 (Table 3), with the caveat that triclosan results demonstrated a slight but significant decline from 2005 to 2008. The NCS results were also similar to those from U.S. women in NHANES 2009–2010 who provided urine specimens during the same time period as the NCS women and also were within the same age range (Supplemental Table), suggesting that exposure to these phenols occurred regardless of pregnancy status. The racial/ethnic differences in concentrations of specific phenols among the NCS women were similar to NHANES and other cohorts of pregnant women. Although the NCS women included relatively small numbers of non-Hispanic blacks, the sample otherwise may be more diverse compared to other U.S. cohorts of pregnant women in which environmental phenols have been measured, allowing us to examine differences in concentrations related to demographic factors and study location. Unfortunately, limited statistical power precluded our ability to assess interactions between study location and demographic covariates of interest. In the NCS women, we found significant positive associations with race/ethnicity for certain phenols: benzophenone-3 (non-Hispanic white); triclosan (Hispanic); 2,4- and 2,5-dichlorophenol (non-Hispanic blacks). That non-Hispanic whites have higher exposures to benzophenone-3 has been noted before (Calafat et al., 2008a) and is likely the result of increased use of benzophenone-3-containing sunscreen agents among this population group compared to others. Median

urinary benzophenone-3 concentrations (Table 4) were considerably lower in the European pregnancy cohorts, possibly related to availability, preference, or both for non-benzophenone-3 containing sunscreen agents, or less widespread use of sunscreens (Casas et al., 2011; Philippat et al., 2012). Explanations for international differences in exposure to phenols or their precursors require information about personal care and consumer product usage. Adjusted urinary triclosan concentrations were higher in Hispanic NCS women than in other women and were also associated with higher education. In the U.S. general population, urinary triclosan concentrations were associated with older age and higher socioeconomic status but not race/ethnicity (Calafat et al., 2008b). Urinary triclosan concentrations in French pregnant women were not examined by demographic factors (Philippat et al., 2012). Adjusted urinary 2,4- and 2,5-dichlorophenol concentrations were higher in non-Hispanic black NCS women. Whether differences in these concentrations reflect racial/ethnic, income, geographic differences (e.g., exposure), or other unmeasured factors requires additional investigation. The NCS main study could collect information on use of products containing target phenols or their precursors so exposure sources, their relative importance, and demographic factors might be explored.

2,4-Dichlorobenzene is a minor contaminant of 1,4-dichlorobenzene, commonly used as a moth repellent and room deodorizer. Because 2,5-dichlorophenol is a major metabolite of 1,4-dichlorobenzene, urinary concentrations of both phenols may reflect exposure to 1,4-dichlorobenzene-containing products, a possibility supported by the correlation between 2,4- and 2,5-dichlorophenol urinary concentrations that we and others have observed (Philippat et al., 2012; Wolff et al., 2008). This possibility also is supported by an earlier NHANES analysis that found higher concentrations of blood paradichlorobenzene in non-Hispanic black adults (Elliott et al, 2006). Among pregnant women studied in the U.S. (Table 4), high urinary 2,4- and 2,5-dichlorophenol concentrations occurred in minority women, generally of lower income and living in highly urban (New York City, NY) or rural agricultural areas (Salinas CA) (Castorina et al., 2010; Wolff et al., 2008). Coincidentally, more than 85% of the non-Hispanic black NCS women also came from the New York City area and a rural county, and they generally reported low annual incomes. We speculate that low income, minority status, or both may be associated with greater use of room deodorizers and moth repellents. In multi-family residences, vapors from these products may enter surrounding units via ventilation ducts, resulting in “passive” or “second-hand” exposure. In lower quality dwelling units, regardless of crowding, there may be greater use of deodorizers and pest repellents. If this is true, then urinary 2,4- and 2,5-dichlorophenol concentrations may be surrogates for quality of living conditions and lower socioeconomic status. Further understanding of the determinants of exposure to these phenols or their precursors is needed, as well as exploration of whether these exposures contribute to adverse health effects or are surrogates for other determinants affecting health outcomes, such as lower birth weight and length that were noted by Wolff et al. (2008).

Urine BPA concentrations in the NCS women were generally similar to those of the NHANES women and U.S. pregnancy cohorts (Supplemental Table, Table 4), and were about 50% lower than those reported in European pregnancy cohorts. The lowest urinary BPA concentrations among those in Table 4 were found in Old Order Mennonite women who had limited exposure to plastics and canned foods. Urinary triclosan concentrations in

the NCS women also were similar to those of NHANES women and the U.S. pregnancy cohort (Supplemental Table, Table 4). Of note, triclosan concentrations in U.S. pregnant women in NHANES 2005–2008 demonstrated a slight but significant downward trend, thus limiting the comparison to NCS results. Urinary MP and PP concentrations were similar overall as well as by racial/ethnic subgroup for the NCS sample and the NHANES groups. A previous analysis of NHANES data found significantly higher urinary MP and PP concentrations in non-Hispanic blacks and was attributed to differences in use of personal care products containing these chemicals (Calafat et al., 2010).

The high detection frequency of the seven phenols in both NHANES and NCS (about 80% or greater) suggests that exposure to these phenols or their precursors among pregnant and non-pregnant women is prevalent. Because these compounds are rapidly metabolized and eliminated in the urine, urinary concentrations reflect recent exposure, and concentrations may fluctuate over a short time period when exposure is intermittent (Braun et al., 2011, 2012; Calafat et al., 2008c; Mahalingaiah et al., 2008; Smith et al., 2012; Ye et al., 2011). This limitation can be minimized by increasing sample size (e.g., NHANES) and varying the urine sampling times over the course of the day. We reduced the analytical variability across the NCS, NHANES, and U.S. cohorts of pregnant women (Table 4) by using the same urine sampling strategy, analytical methods, and laboratory for measuring environmental phenols. The nature of our sample—females within a limited age range—also reduces biological variability related to age and sex. We provide results on a large sample of third trimester women, more than are available in multiple NHANES survey periods, but our study is limited by the nature of the NCS sample and unavailability of exposure information.

5. Conclusions

The CDC collaboration with the NCS demonstrates that with careful planning, detailed protocols, and staff training, high quality biospecimens can be collected across study locations. An important limitation of the current data is lack of exposure information, which the Main Study can overcome. When biospecimens are collected, study visit protocols could gather contemporaneous exposure information (e.g., interviews, environmental sampling, and home observations) that would assist in identifying exposure sources. The Main Study biospecimen plan could obtain repeat biospecimens over time, thereby providing information about variability within individuals and perhaps improving exposure characterization for these and other chemicals that are non-persistent with a short residence time in the body. We believe that including these elements in the Main Study can support a robust analysis of environmental exposures and health outcomes. In the meantime, the Vanguard Study of the NCS can be a valuable source for biomonitoring data in pregnant women, a vulnerable population and currently understudied.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention, the National Institutes of Health, or the U.S. Department of Health and Human Services.

Abbreviations

CCCEH	Columbia Center for Children's Environmental Health
CEHS	Children's Environmental Health Study
CHAMACOS	Center for the Health Assessment of Mothers and Children of Salinas
EDEN	Etude des Determinants pre et post natals du development et de la santé de l'Enfant
HOME	Health Outcomes and Measures of the Environment
INMA	Infancia y Medio Ambiente
PELAGIE	Perturbateurs endocriniens: Étude Longitudinale sur les Anomalies de la Grossesse, l'Infertilité et l'Enfance

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Appendix

The Supplemental Information associated with this article can be found in the online version at:

Table 1

Characteristics of NCS and [a] NHANES Women

Characteristic	NCS N (%)	NHANES 2005–2010 N (%)	NHANES 2009–2010[b] N (%)
Sample Size	506	174	524
Age (years)			
16–29	263 (52.0)	117 (67.2)	281 (53.6)
30–44	243 (48.0)	57 (32.8)	243 (46.4)
Race/ethnicity			
Hispanic	99 (19.6)	72 (41.4)	152 (29.0)
Non-Hispanic white	328 (64.8)	63 (36.2)	231 (44.1)
Non-Hispanic black	30 (5.9)	25 (14.4)	101 (19.3)
Other	49 (9.7)	14 (8.0)	40 (7.6)
Education			
Not high school graduate	136 (26.9)	51 (29.3)	101 (19.3)
High school or some college	157 (31.0)	72 (41.4)	240 (45.8)
College graduate or more	208 (41.1)	34 (19.5)	94 (17.9)
Unknown	5 (1.0)	17 (9.8)	89 (17.0)
[c] Household Income (annual)			
< $50,000	222 (43.9)		
≥ $50,000	229 (45.3)		
< $55,000		122 (70.1)	524 (100)
≥$55,000		44 (25.3)	
Unknown	55 (10.9)	8 (4.6)	
Pregnancy Trimester			not applicable
First		32 (18.4)	
Second		61 (35.1)	
Third	506 (100)	59 (34.0)	
Unknown		22 (12.6)	

[a] NHANES samples and percentages are unweighted.

[b] NHANES 2009–2010 women include all females ages 16–44 years, regardless of pregnancy status.

[c] Household income categories were reported slightly differently for NCS and NHANES.

Table 2

Adjusted Geometric Mean Concentrations of Environmental Phenols in NCS Pregnant Women

		Analyte (μg/L)													
		BP-3		BPA		TCS		MP		PP		2,4-DCP		2,5-DCP	
Category	N	Mean (95% CI)	P-value	Mean (95% CI)	P-value	Mean (95% CI)	P-value	Mean (95% CI)	P-value	Mean (95% CI)	P-value	Mean (95% CI)	P-value	Mean (95% CI)	P-value
All Females	506	59.5 (49.7,71.3)		1.4 (1.2,1.5)		19.0 (16.1,22.4)		103.5 (91.4,117.2)		19.1 (16.1,22.6)		0.70 (0.61,0.80)		3.9 (3.3,4.8)	
Study Site			0.02		0.42		0.2		0.01		0.03		<0.0001		<0.0001
Age (yrs)			0.08		0.06		0.07		0.21		0.64		0.11		0.52
16–29	263														
30–44	243														
Race/ethnicity			0.02		0.12		0.04		0.07		0.42		<0.0001		<0.0001
Non-Hispanic black	30	23.0 (10.8,48.7)				14.2 (6.9,29.2)						1.68 (1.12,2.51)		18.8 (10.3,34.2)	
Non-Hispanic white	328	72.0 (57.0,90.9)				16.4 (13.1,20.5)						0.55 (0.48,0.62)		2.5 (2.1,3.1)	
Hispanic	99	54.0 (33.9,86.2)				33.9 (21.7,63.0)						1.14 (0.89,1.46)		9.0 (6.2,13.0)	
Other	49	36.2 (20.4,64.2)				18.8 (10.9,32.5)						0.74 (0.54,1.0)		5.3 (3.4,8.4)	
Education			0.02		0.77		0.04		0.06		0.04		0.08		0.04
Income			0.38		0.47		0.29		0.8		0.15		0.77		0.48
Urine creatinine			<0.0001		<0.0001		<0.0001		<0.0001		<0.0001		<0.0001		<0.0001

Overall geometric means are presented for All Females. Adjusted geometric means are shown for subgroups when race/ethnicity was significant ($p<0.05$) in the regression analysis, using the covariates study site, age, race/ethnicity, education, income, and log urinary creatinine. Study site was frequently significant, but age was not for any of the urine phenol results.

Detection frequencies were benzophenone-3 (BP-3) 100%, BPA 89.1%, triclosan (TCS) 81%, Methyl paraben (MP) 100%, Propyl paraben (PP) 98.4%, 2,4-dichlorophenol (2,4-DCP) 82.8%, and 2,5-dichlorophenol (2,5-DCP) 94.1%.

Table 3

Concentrations of Urinary Phenols (μg/L) in NCS Pregnant Women and Pregnant Women in the U.S. (NHANES 2005–2010)

	NCS Pregnant Women (Total = 506)		Pregnant Women in the U.S. (Total = 174)	
Analyte	**Geometric Mean (95% CI)**	**50th Percentile (95% CI)**	**Geometric Mean (95% CI)**	**50th Percentile (95% CI)**
Bisphenol A	1.4 (1.2–1.5)	1.3 (1.2–1.5)	1.5 (1.3–1.8)	1.3 (1.1–2.0)
Benzophenone-3	59.5 (49.7–71.3)	42.9 (33.3–57.7)	38.9 (24.5–61.6)	26.5 (14.1–78.8)
Triclosan	19.0 (16.1–22.4)	15.6 (12.0–21.7)	[a]28.85 (18.78–44.32)	[a]24.72 (15.45–39.13)
Methyl paraben	103.5 (91.4–117.2)	105.5 (88.3–131.0)	103.5 (68.4–156.5)	84.7 (61.7–151.4)
Propyl paraben	19.1 (16.1–22.6)	22.3 (19.1–27.5)	18.7 (11.0–31.9)	20.6 (12.6–26.4)
2,4-Dichlorophenol	0.7 (0.7–0.8)	0.6 (0.5–0.7)	0.6 (0.5–0.9)	0.5 (0.4–0.6)
2,5-Dichlorophenol	3.9 (3.3–4.8)	2.7 (2.2–3.3)	5.6 (3.2–10.0)	4.8 2.4–7.2)

[a]Results for Triclosan in pregnant women in the U.S. showed a slight but significant decline from NHANES 2005–2008.

Table 4

Median Urinary Concentrations of Phenols in Pregnant Women

Description and time of sample collection	Sample size	Urine collection (trimester)	Median concentration (μg/L)[a]							Characteristics of women or cohort
			BP-3	BPA	TCS	MP	PP	2,4-DCP	2,5-DCP	
NCS 2009–2010 (present study)	506	3rd	42.9	1.3	15.6	105.5	22.3	0.6	2.7	Convenience sample of Vanguard Center enrollees
NHANES 2005–2010 (present study)	174	any	26.5	1.3	17.7	84.7	20.6	0.5	4.8	U.S. general population
EDEN and PELAGIE cohorts (Philippat et al, 2012)	191	any	1.3	2.7	24.1	97.8	12.5	0.9	10.2	Nested case-control study drawn from both cohorts
Old Order Mennonite women (Martina et al, 2012)	10	2nd–3rd	na	0.7	na	na	na	na	na	Diet is largely fresh dairy and produce
Japanese women (Shirai et al, 2012)	111	any	na	na	na	75.8	20.2	na	na	Delivered at one Tokyo hospital
INMA cohort (Casas et al, 2011)	120	3rd	3.4	2.2	6.1	na	na	1.1	16.5	Reside in one of 5 cities in Spain
CHAMACOS cohort (Castorina et al, 2010)	523, 478	early 2nd, 3rd	na	na	na	na	na	1.8 1.1	21.5 18.5	Reside in agricultural area of California; majority Hispanic; 2 samples per woman
Mexico City cohort Cantonwine et al, 2010)	60	3rd	na	0.95	na	na	na	na	na	Attend IMSS prenatal clinic
Women planning pregnancy (Smith et al 2012)	129	any	na	na	na	135	22.8	na	na	Infertility clinic attendees; 2–3 samples per woman
Japanese women (Fujimaki et al 2004)	56	any	na	<LOD	na	na	na	na	na	Delivered at one Tokyo hospital; LOD=1.1 μg/L; 30% >LOD
CCCEH cohort (Perera et al, 2012)	198	3rd	na	1.96[b]	na	na	na	na	na	Reside in NYC and African-American or Dominican
CEHS cohort (Wolff et al, 2008)	367	3rd	7.5	1.3	11	na	na	2.1	53	New York City residents; majority non-white (Hispanic or black)
Generation R cohort (Ye et al, 2008)	100	3rd	na	1.2	na	na	na	na	na	Reside within study area in Rotterdam, the Netherlands
HOME cohort (Braun et al, 2009)	332	early 2nd, early 3rd, birth	na	1.8 1.7 1.3	na	na	na	na	na	Reside in Cincinnati, OH in pre-1978 housing; 3 visits per woman

Abbreviations: BP-3, benzophenone-3; BPA, bisphenol A; TCS, triclosan; MP, methyl paraben; PP, propyl paraben; 2,4-DCP, 2,4-dichlorophenol; 2,5-DCP, 2,5-dichlorophenol. LOD = limit of detection; na = not available.

[a] LODs for analytes were the same, with analyses performed by the same laboratory, except for Ye, et al. (BPA = 0.26 μg/L); Shirai et al (MP=0.57 and PP=0.48 μg/L);

[b] mean concentration